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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,216	NICOLETTE, CHARLES A.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *4-9 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1 and 9 have been amended, and claims 10-16 are new.

The new claims 14, and 16 are directed to a composition comprising antigen-specific cells, which is group IV. The inventions are distinct, each from the other because of the following reasons: Inventions the examined group I and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions the main active ingredient in their respective compositions have different biological functions.

Claims 13, 15, and 16 are directed to method of making CLT ex vivo using the claimed peptides, which is group V. The inventions are distinct, each from the other because of the following reasons: Inventions I and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of group III.

Claims 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 4-9 remain withdrawn for reason of record from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The request for rejoining the method claims are noted, but the request is denied because the composition claims are allowable with this Office action.

Claims 1-16 are pending, and claims 1-3 and 10-12 are under consideration.

This Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claims 1-3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 101, Withdrawn

The rejection of claim 1 under 35 USC 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102, Withdrawn

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Asano et al., J Biol Chem. 1997 Oct 24;272(43):27042-52) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Asano et al.,(cited above) in view of US 5789200 A (Aug. 4, 1998) is withdrawn because the amended claims are not obvious over the prior art of record.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3 are drawn to a composition comprising at least two ligands, wherein each of the claimed ligands in the composition is selected from SEQ ID NOs: 3, 5, 7, 9, and 11, claim 10 is drawn to the composition comprising a ligand wherein the igand is selected from SEQ ID NOs: 3, 5, 7, and 9, claims 11 further comprises SEQ ID: 11 in addition to the composition in claim 11, and claim 12 is drawn to a composition comprising a ligand consisting of SEQ ID NO: 11.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the

art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification at page 10, 3rd paragraph discloses that the claimed invention is used for eliciting immune responses, especially cell-mediated via T cell activation, and at page 7 lines 23-26 discloses that self-antigen induces little or no immune response in the subject due to self-tolerance to the antigen. The specification is mostly about review of how a tumor antigen could be used for T cell epitope with MHC molecules. The specification does not discloses whether SEQ ID NOs: 3, 5, 7, 9, or 11 is a fragment of a tumor antigen or not.

Search of the claimed SEQ ID NOs reveals that SEQ ID NO: 11 is a self-antigen, i.e. an internal fragment of elf3-p40 shown in Fig 5B of Asano et al., of record at page 27047 (also note Fig. 3B). Neither the specification nor any art of record teaches whether SEQ ID NOs: 3, 5, 7, and/or 9 is a fragment of a tumor antigen expressed in or on cancer cells. The specification at page 5 lines 6-10 contemplates that the synthetic peptides (SEQ ID NOs 3, 5, 7, and 9) are used to induce an immune response to the same native ligand. However, neither the specification nor any art of record teaches whether SEQ ID NOs 3, 5, 7, and 9 would induce an immune response to the same native ligand. The specification does not establish which entity is "the same native ligand" of SEQ ID NOs 3, 5, 7, and 9, although the specification asserts the individual ligands of SEQ ID NOs: 3, 5, 7, 9 are synthetic analogues of the naturally occurring peptide epitope of elf3-p40, an asserted potential tumor antigen, namely the peptide epitope ("ligand") of SEQ ID NO: 11 peptide. The specification mostly contemplates

that T cell responses may be elicited by using the claimed peptides in context of MHC molecules, thereby stimulating proliferation of cytolytic T cells in the subject. It is not clear if (CTLs) could be generated using any of the claimed SEQ ID Nos.

The specification, however, does not show that the ligands of SEQ ID NOs: 3, 5, 7, and 9 have increased binding affinity to any MHC molecule, nor does the specification show these ligands are able to elicit an immune response against the native ligand comprising SEQ ID NO: 11 or against the native ligand, elf3-p40.

Based on the disclosure of the specification, it is concluded that the claimed invention cannot be used without the need to perform an additional amount of undue experimentation because the specification does not teach whether each of the individual "ligands", which herein are alternatively referred to as "peptides" or "peptide epitopes", is able to elicit an immune response against the native peptide epitope of SEQ ID NO: 11 and the natural, intact elf3-p40 protein. If even the intact elf3-p40 protein comprising the instant SEQ ID NO: 11 is a tumor antigen as suggested in the instant application, the ligands of SEQ ID NOs: 3, 5, 7, and 9 differ from the ligand of SEQ ID NO: 11 at every position but the last; thus, SEQ ID NOs: SEQ ID NOs: 3, 5, 7, and 9 are only similar to SEQ ID NO: 11 in that all have a valine residue at the carboxy-terminus. Because the ligands of SEQ ID NOs: SEQ ID NOs: 3, 5, 7, and 9 bear no apparent substantial structural similarity to SEQ ID NO: 11, and because the art teaches that the specific immunogenicity of peptides cannot be reliably predicted, as further explained below, one skilled in the art could not use the claimed invention without first having to characterize the ligands of SEQ ID NOs: 3, 5, 7, and 9 as able to elicit an immune

response against the ligand of SEQ ID NO: 11 and/or the native elf3-p40 polypeptide comprising SEQ ID NO: 11.

The results of searching relevant sequence databases using any of SEQ ID NOs: 3, 5, 7, and 9 as a query fail to suggest that these sequence map to any portion of the amino acid sequence of elf3-p40 protein or any other tumor antigen for that matter. Because none of SEQ ID NOs: 3, 5, 7, and 9 appear to be fragments of the amino acid sequence of the native elf3-p40, or analogues thereof, none would be reasonably expected to produce an immune response against elf3-p40 as asserted in the specification for the use of the claimed invention.

Guichard et al. (*J. Med. Chem.* 2000; **43**: 3803-3808), for example, teaches they and others were surprised to discover that in the case of the MART-1 peptide epitope, which maps to amino acids 27-35 of the native MART-1 antigen, the substitution of alanine by leucine or methionine at the second position ("P2"), although considerably improving binding to HLA-A2, resulted in a dramatic reduction of the peptide's ability to stimulate an immune response (paragraph bridging pages 3803 and 3804).

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature, since, for example, Bowie et al. (*Science*. 1990 Mar 16; **247** (4948): 1306-1310) teaches the skilled artisan cannot reliably predict which variants of a native protein function similarly to the native protein, and which do not, because the prediction of a protein's propensity to form a particular structure, and to subsequently infer detailed aspects of function from the predicted structure, is extremely complex; see entire document (e.g., page 1306, column 1). Furthermore, Bowie et al.

teaches, while it is known that many amino acid substitutions are possible in any given protein, and proteins are surprisingly tolerant of amino acid substitutions, the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited, particularly at positions where the amino acid residues have critical roles in the protein's structure and function, and these regions can tolerate only conservative substitutions, or none at all (page 1306, column 2).

Although Schirle et al. (*J. Immunol. Methods.* 2001; **257**: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

US Pat. 5,840,839 (Nov. 24, 1998) teach at column 19 that finding a peptide that binds to a MHC molecules and stimulates immune response is not a trivial matter. The

'839 patent at column 19, lines 53 to 67 teaches that structure a T cell epitope that stimulates immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

Moreover, Anderson et al. (*Tissue Antigens*. 2000 Jun; **55** (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (*Mol. Immunol.* 1994 Dec; **31** (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune

response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

van der Burg et al. (*J. Immunol.* 1996 May 1; **156** (9): 3308-3314) teaches that the immunogenicity of peptides bound to MHC class I molecules depends on the stability of the complex, not just the binding affinity; see entire document (e.g., the abstract). Moreover, van der Burg et al. teaches that the immunogenicity of peptide epitopes can be more accurately predicted by their dissociation rate, as opposed to the MHC class I binding affinity; see, e.g., the abstract.

Thus, even if each of the individual peptides of the claimed invention were to have greater HLA-A2 binding affinity than the naturally occurring peptide epitope of SEQ ID NO: 25, the invention could be still not be used to stimulate an immune response against the peptide of SEQ ID NO: 25 or against the native MART-1 polypeptide without first performing an undue amount of experimentation, since it would still be necessary to determine if the analogues are capable of stimulating an immune response against the native protein or it natural peptide epitope of SEQ ID NO: 25.

As such, it is noted that Valmori et al. (*Journal of Immunology.* 1998; **160**: 1750-1758), for example, teaches analogues of SEQ ID NO: 25 that bound more efficiently than the natural peptide epitope, but which were poorly recognized by tumor reactive cytotoxic T lymphocytes (CTL); see entire document (e.g., the abstract). Because the analogues were poorly recognized by antigen-specific CTL, the analogues could not

effectively elicit an immune response against the native MART-1 antigen, or against tumor cells expressing the antigen.

Finally, it is noted that the specification asserts the claimed invention can be used therapeutically. The specification fails to teach how administration of composition comprising the claimed peptide, especially comprising the self-antigen of SEQ ID NO: 11 would produce a sufficient amount of CTLs, NK cells and/or any other T cells to kill tumors in an animal or human that has malignant cells expressing elf3-p40 shown in Fig 5B disclosed in Asano et al. Asano et al., of record teaches the protein comprising the instant SEQ ID NO: 11 is a self antigen, rather than a mutated antigen, as it is expressed on normal tissues. The specification does not teach other claimed peptides are from mutated elf3-p40 found on cancer cells.

The objective of using the claimed composition therapeutically would be to stimulate the proliferation of cytotoxic T cells (CTL) that are reactive against any tumor expressing the native ligand. However, Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden; see entire document (e.g., page 206, paragraph 2). Boon teaches the establishment of immune tolerance may therefore have already occurred in the patient; and in such cases, active specific immunization will be fruitless, since anergic CTL cannot be activated, will not proliferate, and are deficient in effector function (page 206, paragraph 2). Thus, while a ligand might stimulate an effective immune response in one patient having a low tumor burden, perhaps, it is entirely possible that the ligand

will not be immunogenic in another. Accordingly, the skilled artisan cannot predict whether each of the peptide analogues of which the claimed composition is composed will individually elicit an immune response against the native epitope or antigen in a patient carrying a large tumor burden; and therefore, the skilled artisan could not use the claimed invention without having to first perform an undue amount of additional experimentation to determine if the analogues are each capable of doing so.

Self-tolerance may eliminate T cells that are capable of recognizing self-antigen with high avidity (Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the

plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two

T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule.

Based on the references discussed above, that the state of the art with respect to method of generating T-cell immune response in vivo against self-antigen is unpredictable, and the specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs, no working examples in the specification, and upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the preponderance of factual evidence of record indicates the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation to determine if each of the individual ligands of which the claimed composition are able to stimulate an effective immune response against the native ligand of SEQ ID NO: 11 or the native, intact elf3-p40.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-

272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642